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TITLE: Inhibition of the degradation of connective tissue matrix protein components in mammals
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EXEMPLARY CLAIM: 1
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AB . . . rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

SUMM . . . deficiency syndrome (AIDS), burns, wounds such as bed sores and varicose ulcers, fractures, trauma, gastric ulceration, skin diseases such as **acne** and psoriasis, lichenoid lesions, epidermolysis bollosa, aftae (reactive oral ulcer), dental diseases such as periodontal diseases, peri-implantitis, cysts and root. . .

SUMM . . . which are useful in the method of the present invention include bisphosphonates which are active as inhibitors against matrix metalloproteinases (**MMPs**), especially against one or both of the following **MMPs**: **MMP**-1 and **MMP**-8, both of which have a significant impact on the protein degradation system in mammals in inflammatory and other diseases (Krane,. . .

SUMM Examples of suitable bisphosphonates include commercially available bisphosphonates such as **clodronate**, **etidronate**, **pamidronate**, **tiludronate**, etc. An especially preferred bisphosphonate for use in the present invention is **clodronate** which has been shown to inhibit the activity of **MMP**-1 and **MMP**-8.

SUMM . . . arthritis, gastric ulceration, burns, wounds such as bed sores and varicose ulcers, fractures, trauma, gastric ulceration, skin diseases such as **acne** and psoriasis, lichenoid lesions, epidermolysis bollosa, aftae (reactive oral ulcer), dental diseases such as periodontal disease, periodontitis, peri-implantitis and root. . .

DRWD FIG. 1 is a block graph of the effects of **clodronate** on purified human fibroblast-type collagenase (**MMP**-1) activity;

DRWD FIG. 2 is a block graph of the effects of **clodronate** on collagenase activity present in jaw cyst extracts;

DRWD FIG. 3 is a block graph of the effects of **clodronate** on human neutrophil collagenase (**MMP**-8) activity;

DRWD FIG. 4 is a block graph of the effects of **clodronate** on the

collagenase activity in gingival crevicular fluid of human adult periodontitis patients; and

DETD . . . gastrointestinal intolerability, especially with some amino derivatives and inhibition of normal mineralization. One significant negative side effect of bis-phosphonates, especially **etidronate**, in prolonged administration is generally related to their activity on bone, i.e. they not only stop the resorption of bone,. . . a desired effect as anti-osteolytic agent, but they may also prevent mineralization entirely, and this is the reason that especially **etidronate** is normally administered only for a short term followed by a delay of three months.

DETD . . . mammalian matrix protein degradation in the connective tissue system according to the present invention is an amount that significantly reduces **MMP** activity. In the preferred embodiment of the present invention, the bisphosphonate is administered in an amount sufficient to significantly reduce the activity of the collagenases **MMP**-1 and **MMP**-8.

DETD . . . of an ulceration of the cornea, the lungs in the case of lung cancer, the skin in the case of **acne** or psoriasis or skin diseases involving tissue destruction such as bed sores, varicose ulcers, etc.

DETD Inhibition of Purified Human Fibroblast collagenase (**MMP**-1) by **clodronate**

DETD Purified trypsin-activated human fibroblast-type **MMP**-1 (Konttinen et al., Matrix, 11:395-403; for trypsin-activation of latent pro-**MMPs**, see Sorsa et al., Med. Biol. 63:66-72, 1985) was incubated with purified 1.5 .mu.M type I collagen in different indicated **clodronate** concentrations and buffer for 20 hours at 22.degree. C. Preincubations of **MMP**-1 with the buffer and

L12 ANSWER 3 OF 3 USPATFULL

CLM What is claimed is:

1. A method of reducing of reducing a pathological excess of mammalian collagenolytic enzyme activity and an excessive degradation of connective tissue matrix protein components in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the matrix metalloproteinase (NMP) activity in said mammal.

2. The method of claim 1, which comprises administering to said mammal an effective amount of bisphosphonate which results in a significant reduction of the MMP dependent protein degradation in said mammal.

3. The method of claim 1, wherein said bisphosphonates comprises a bisphosphonate which is active as an inhibitor against at least one matrix metalloproteinase (MMP).

4. The method of claim 3, wherein said matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8 and a combination of MMP-1 and MMP-8, and wherein said mammal is a human having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8.

5. The method of claim 1, wherein said bisphosponate is a geminal bisphosphonate having the general formula ##STR2## wherein R' and R" independently stand for a hydrogen or a halogen atom, a hydroxy, optionally substituted amino or optionally substituted thio group or an optionally substituted hydrocarbon residue.

6. The method of claim 5, wherein said bisphosphonate is selected from the group consisting of (1-hydroxyethylidene)bis-phosphonate, (dichloromethylene)bis-phosphonate (clodronate), (3-amino-1-hydroxypropylidene)bisphosphonate, (4-amino-1-hydroxybutylidene)bis-phosphonate, {[4-chlorophenyl)thio]methylene}bis-phosphonate, (6-amino-1-hydroxyhexylidene)bis-phosphonate, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-phosphonate, [3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate, [1-hydroxy-3-(methylpentylamino)propylidene]bis-phosphonate or a mixture thereof.

7. The method of claim 6, wherein said bisphosphonate is clodronate.

8. The method of claim 1, wherein said bisphosphonate is administered in a way selected from the group consisting of oral, intravenous, parenteral, subcutaneous and topical administration.

9. The method of claim 1 wherein said mammal is a human selected from a populace susceptible to an excess degradation of connective tissue matrix protein components selected from the group consisting of diabetics and health care workers, and wherein said bis-phosphonate is administered prophylactically.

10. The method of claim 1 wherein said mammal is a human, with the proviso that such human is not (a) a patient in need of a skeletal marker in the form of .sup.99m technetium derivatives for diagnostic purposes in nuclear medicine, (b) a patient in need of administration of an anti-osteolytic agent, (c) a patient with ectopic calcification and ossification in need of an inhibitor of calcification, or (d) a patient in need of an anti-tartar agent.

11. The method according to claim 10 wherein said human is a patient selected from the group of patients in need of treatment of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

12. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises a physiological or pathological condition selected from the group consisting of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

13. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises periodontitis.

14. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises peri-implantitis.

15. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises cancer and metastasis progression in connective tissues.

16. A method of inhibiting extracellular activity of MMP-1, MMP-8 or both MMP-1 and MMP-8, in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the extracellular matrix MMP-1, MMP-8 or both MMP-1 and MMP-8 activity in said mammal.

17. A method according to claim 16 wherein said mammal is a human patient having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8 and is in need of a treatment selected from the group consisting of treatments of wounds, burns, lesions, ulcers, rheumatoid arthritis

or

other arthritides, cysts, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne** and psoriasis.

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L12 ANSWER 3 OF 3 USPATFULL

CLM What is claimed is:

1. A method of reducing of reducing a pathological excess of mammalian collagenolytic enzyme activity and an excessive degradation of connective tissue matrix protein components in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the matrix metalloproteinase (NMP) activity in said mammal.

2. The method of claim 1, which comprises administering to said mammal an effective amount of bisphosphonate which results in a significant reduction of the MMP dependent protein degradation in said mammal.

3. The method of claim 1, wherein said bisphosphonates comprises a bisphosphonate which is active as an inhibitor against at least one matrix metalloproteinase (MMP).

4. The method of claim 3, wherein said matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8 and a combination of MMP-1 and MMP-8, and wherein said mammal is a human having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8.

5. The method of claim 1, wherein said bisphosponate is a geminal bisphosphonate having the general formula ##STR2## wherein R' and R" independently stand for a hydrogen or a halogen atom, a hydroxy, optionally substituted amino or optionally substituted thio group or an optionally substituted hydrocarbon residue.

6. The method of claim 5, wherein said bisphosphonate is selected from the group consisting of (1-hydroxyethylidene)bis-phosphonate, (dichloromethylene)bis-phosphonate (clodronate), (3-amino-1-hydroxypropylidene)bisphosphonate, (4-amino-1-hydroxybutylidene)bis-phosphonate, {[4-chlorophenyl)thio]methylene}bis-phosphonate, (6-amino-1-hydroxyhexylidene)bis-phosphonate, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-phosphonate, [3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate, [1-hydroxy-3-(methylpentylamino)propylidene]bis-phosphonate or a mixture thereof.

7. The method of claim 6, wherein said bisphosphonate is clodronate.

8. The method of claim 1, wherein said bisphosphonate is administered in a way selected from the group consisting of oral, intravenous, parenteral, subcutaneous and topical administration.

9. The method of claim 1 wherein said mammal is a human selected from a populace susceptible to an excess degradation of connective tissue matrix protein components selected from the group consisting of diabetics and health care workers, and wherein said bis-phosphonate is administered prophylactically.

10. The method of claim 1 wherein said mammal is a human, with the proviso that such human is not (a) a patient in need of a skeletal marker in the form of .sup.99m technetium derivatives for diagnostic purposes in nuclear medicine, (b) a patient in need of administration of an anti-osteolytic agent, (c) a patient with ectopic calcification and ossification in need of an inhibitor of calcification, or (d) a patient in need of an anti-tartar agent.

11. The method according to claim 10 wherein said human is a patient selected from the group of patients in need of treatment of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

12. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises a physiological or pathological condition selected from the group consisting of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne**, psoriasis, loosening of end-osseal hip-protheses.

13. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises periodontitis.

14. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises peri-implantitis.

15. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises cancer and metastasis progression in connective tissues.

16. A method of inhibiting extracellular activity of MMP-1, MMP-8 or both MMP-1 and MMP-8, in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the extracellular matrix MMP-1, MMP-8 or both MMP-1 and MMP-8 activity in said mammal.

17. A method according to claim 16 wherein said mammal is a human patient having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8 and is in need of a treatment selected from the group consisting of treatments of wounds, burns, lesions, ulcers, rheumatoid arthritis or other arthritides, cysts, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, **acne** and psoriasis.

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L19 ANSWER 3 OF 182 CAPLUS COPYRIGHT 2001 ACS
TI The role of **salicylic acid** in the **antioxidant** signal transduction pathway
AB **Antioxidant** enzyme activity was measured in salt tolerant callus tissue derived from the cultivar Coker 312 over an 8 h period following treatment with either 0.1.mu. M paraquat, 10 mM H2O2 or 100 .mu.M **salicylic acid**. Paraquat induced in up-regulation of catalase, peroxidase, ascorbate peroxidase, and glutathione reductase activities within 1 h after treatment. The H2O2 and **salicylic acid** treatments resulted in significant increases in peroxidase and glutathione reductase within 2 h and in catalase and ascorbate reductase within 8 h. These data suggest that **salicylic acid** induces an **antioxidant** response through a pathway medicated by H2O2.
IT Signal transduction, biological
(**antioxidant**; role of **salicylic acid** in **antioxidant** signal transduction pathway in cotton)
IT Enzymes, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**antioxidant**; role of **salicylic acid** in **antioxidant** signal transduction pathway in cotton)
IT Cotton
(role of **salicylic acid** in **antioxidant** signal transduction pathway in cotton)
IT 69-72-7, **Salicylic acid**, biological studies
4685-14-7, Paraquat 7722-84-1, Hydrogen peroxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(role of **salicylic acid** in **antioxidant** signal transduction pathway in cotton)
IT 9001-05-2, Catalase 9001-48-3, Glutathione reductase 9003-99-0, Peroxidase 72906-87-7, Ascorbate peroxidase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(role of **salicylic acid** in **antioxidant** signal transduction pathway in cotton)

L19 ANSWER 4 OF 182 CAPLUS COPYRIGHT 2001 ACS
IT 59-02-9, .alpha.-Tocopherol 69-72-7, **Salicylic acid**, biological studies 99-50-3, Protocatechuic acid 99-96-7, p-Hydroxybenzoic acid, biological studies 117-39-5, Quercetin 119-13-1, .delta.-Tocopherol 121-34-6, Vanillic acid 149-91-7, Gallic acid, biological studies 153-18-4, Rutin 154-23-4, (+)Catechin 327-97-9, Chlorogenic acid 331-39-5, Caffeic acid 480-41-1, Naringenin 490-46-0, (-)-Epicatechin 490-79-9, Gentisic acid 529-44-2, Myricetin 530-57-4, Syringic acid 530-59-6, Sinapic acid 552-58-9, Eriodictyol 970-74-1, (-)-Epigallocatechin 1135-24-6, Ferulic acid 7400-08-0, p-Coumaric acid 7616-22-0, .gamma.-Tocopherol 21637-25-2, Isoquercitrin 23567-23-9, Procyanidin B3 78362-05-7, Prodelphinidin B3
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); ANST (Analytical study); BIOL (Biological study)
(detn. of **antioxidant** activity of phenolic compds. by coulometric detection)

L18 ANSWER 15 OF 72 USPATFULL

CLM What is claimed is:

1. A method for treating **acne** vulgaris comprising applying to the skin of a subject having this condition a therapeutically effective of salicylic acid and **benzoyl peroxide** for a period of time sufficient to alleviate symptoms of said **acne** condition, said salicylic acid being applied at a concentration in the range of from about 3% to 7% by weight and said **benzoyl peroxide** being applied at a concentration of about 3% to 20% by weight; said percentages being expressed on a weight basis based on the total weight of compositions containing said **benzoyl peroxide** or salicylic acid or the combination of **benzoyl peroxide** and salicylic acid.

. . . claim 1 in which the concentration of the salicylic acid is about 5% by weight and the concentration of the **benzoyl peroxide** is about 5% by weight.